REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 45-52 and 55-70 are in the case.

I. ELECTION/RESTRICTION

The election of Group III is hereby affirmed. Claims 1-44 have been cancelled without prejudice to the possibility of pursuing the subject matter of those claims in a separate divisional application.

II. INFORMATION DISCLOSURE STATEMENT

Copies of the references to Lloyd et al and Gerlach et al are enclosed with the present response together with a further Information Disclosure Statement. It is requested that the attached Information Disclosure Statement be initialed and a copy returned to the undersigned with the next paper to issue in this application.

III. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 45-70 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. In response and without conceding to the merit of this rejection, the claims have been amended to take account of the Examiner's formal points. The following comments are offered.

Claim 45 has been amended to take account of the alleged lack of antecedent basis for "the cell biomass" and "circulation means being responsive to the cell

biomass". Support for the amendments can be found in the specification at page 3, lines 13-20 and in original claim 53. Claim 53 has been cancelled without prejudice.

With regard to the rejection of claim 51, the specification refers to the "radius" of the hollow fibers being in the range of 100 to 400 microns (see page 4, lines 16-19 and page 12, lines 19-20). Claim 51 has accordingly been amended to replace the term "diameter" with "radius".

With regard to claim 53, the subject matter of that claim has now been incorporated into claim 45. Claim 53 has accordingly been cancelled without prejudice, thereby rendering moot the rejection of that claim.

Withdrawal of the outstanding 35 U.S.C. §112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

IV. THE OBVIOUSNESS REJECTIONS

Claims 45-53, 55-58 and 60-70 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5, 763,194 to Slowiaczek et al in view of U.S. Patent 5,202,254 to Amiot et al. Claim 54 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Slowiaczek et al in view of Amiot et al and further in view of U.S. Patent 5,252,216 to Folena-Wasserman et al. Claim 59 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Slowiaczek et al in view of Amiot et al and further in view of U.S. Patent 5,126,238 to Gebhart et al. Those rejections are respectfully traversed.

The invention of the present application provides a bioreactor for the proliferation and growth of cells. The bioreactor comprises a plurality of hollow fibres for

containment of cells therein and formed from a semipermeable material that is permeable to at least one substance selected from a nutrient, a regulator and a metabolite but is substantially impermeable to at least one protein required for proliferation, differentiation and/or genetic modification. The hollow fibres are positioned within a housing defining an acellular space. Housing inlet and housing outlet means communicate through the acellular space to define an acellular flow path, and a liquid flow circuit provides fluid communication between the housing inlet and outlet means. Circulation means are associated with the liquid flow circuit to circulate media through the acellular space, and the media is circulated by the circulation means at a rate responsive to the oxygen uptake, metabolite uptake and/or lactate output of the cells.

Slowiaczek describes a cell separation method for removing a desired cell type from a sample of cells which include the desired cell type. The method is based on binding the desired cell type to a ligand present on a device which includes a semipermeable substrate. Cells which do not bind are removed by low sheer stress, whereas bound cells are removed by high sheer stress. The focus of Slowiaczek is therefore on cell separation rather than on cell culture, which is the focus of the present invention.

Although Slowiaczek states (column 3, lines 11-15) that the bound cells may be maintained under conditions in which the cells may divide and multiply, this does not suggest that the cells may be grown to concentrations considerably greater than conventional culture systems by the provision of the semi-permeable material being permeable to at least one nutrient, regulator or metabolite but not permeable to at least one protein required for proliferation. Nor is there any suggestion that the perfusion rate

is controlled to balance oxygen uptake etc with the cellular biomass.

Amiot fails to cure the above-noted deficiencies of Slowiaczek. Amiot describes a method for culturing cells in a bioreactor. The method differs from the method of the present invention in two respects. First, the cells are inoculated into the extracapilliary space of the bioreactor (see column 4, lines 59-62), as opposed to residing within the lumen of the hollow fibers, as in the present invention. Secondly, the method requires two media circulation loops, a first media is circulated through the lumens of the capillary fibres and a second media is circulated through the extracapilliary space of the bioreactor.

Neither Slowiaczek nor Amiot, either alone or in combination, discloses or suggests the advantages of the present invention. Neither citation discloses or suggests the advantages of intracapillary growth of cells for cell expansion. In fact, Amiot leads away from the present invention in that the cells are grown on the extracapillary side of the fibres. Furthermore, the device of the present Invention provides for ease of scale-up because of the intracapillary growth of cells and requirement for less media since there is only a single media circulation through the bioreactor. The flow path of the media along the intracapillary side of a hollow fibre semi-permeable membrane is uniform because the flow is equally distributed along the inside of the fibres.

In contrast, the extracapillary flow pattern is complex and unpredictable because the media has to flow around a hollow fibre bundle with irregular external geometry. This results in the formation of eddies with regions of low flow rate, if cells are grown on the extracapillary side of the membrane, it is not possible to inoculate and harvest cells

with such high efficiency because the flow is non-uniform. The consequence is that there is non-uniform distribution of cells within the bioreactor and difficulties in recovering cells from low flow regions.

If cells are inoculated into the extracapillary side of the hollow fibres, many cells deposit on the inside of the shell encasing the hollow fibres, well away from the surface of the hollow fibres. By contrast. intracapillary cell inoculation results in cell deposition onto the hollow fibre membrane. The diffusion distances between fresh media and cells is uniform and predictable because cells are separated from the well mixed extracapillary media by a membrane with uniform dimensions. This results in homogenous mass transfer with higher cell viability compared to extracapillary cell growth.

It is clear from the above that Slowiaczek and Amiot do not suggest to one of ordinary skill in the art the present invention embodying the features of (a) intracapillary growth of cells, (b) a single flow path of media through the extracapillary space, (c) circulation that is responsive to cellular biomass and (d) integration of cell separation and expansion as a single platform. Clearly, therefore, one of ordinary skill would not have been motivated to combine the disclosures of Slowiaczek and Amiot in the context the presently claimed invention. Absent any such motivation, a *prima facie* case of obviousness has not been generated in this case. Reconsideration and withdrawal of the outstanding obviousness rejection of claims 45-53, 55-58 and 60-70 are accordingly respectfully requested.

With reference to the obviousness rejection of claim 54, that claim has been cancelled without prejudice. Withdrawal of the obviousness rejection of that claim is now respectfully requested.

With reference to claim 59, that claim is dependent on claim 45 and thereby incorporates all of the features of claim 45 which are clearly patentably distinguished over Slowiaczek and Amiot for the above-discussed reasons. Gebhard does not cure the deficiencies of Slowiaczek and Amiot, and does not give rise to *prima facie* case of obviousness of the subject matter of claim 59. Withdrawal of this obviousness rejection is accordingly respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

Attachments: References of Lloyd et al and Gerlach et al
Information Disclosure Statement; PTO/SB/08a